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Clinical Observations of Axillary Involvement for Tubular, Lobular, and Ductal Carcinomas of the Breast

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Background and Objectives: Recently, there has been much interest in identifying primary breast cancer characteristics which have predictive value for axillary metastases. We studied breast cancer patients to determine variables associated with the incidence/extent of axillary involvement and to construct a modeled analysis.

Methods: Patients with invasive ductal, lobular, and tubular breast cancer (group 1, n = 15,719) were analyzed by tumor size and histology for the probability/extent of axillary metastases. A subgroup of patients was analyzed separately for any association of axillary involvement and other variables (group 2).

Results: In group 1, the incidence and extent (number of positive lymph nodes) of axillary metastases correlated significantly with histology and increasing tumor size of ductal and lobular histologies. Significant associations for ⩽10% axillary involvement in group 2 were age and S phase for tubular histology and differentiation for ductal histology. In a multivariate analysis, increasing tumor size was the only statistically significant correlate for axillary involvement (group 2) and for increasing number of positive nodes (group 1).

Conclusions: A multivariate model of tumor size and age combined with staging techniques can successfully confirm or assess extent of axillary metastases in breast carcinoma.

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KEY WORDS: **breast neoplasm; axilla; dissection; lobular carcinoma; tubular carcinoma; infiltrating duct carcinoma**

INTRODUCTION

Axillary dissections traditionally have been an important tool for staging breast cancer. Although its survival benefits have been questioned [1], this surgical procedure decreases axillary recurrences, especially in women with clinically positive nodes. Recently, there have been doubts concerning its usefulness to determine adjuvant therapy for clinically node-negative patients with an early carcinoma of the breast. However, despite recent developments in prognostic markers, axillary status remains the most significant prognostic variable. The therapy of women who would not receive additional treatment because of favorable primary tumor prognostic

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TABLE I. Patient Characteristics for Group 1 (Total of 15,719 Patients From the State of Colorado Cancer Registry)

Group 1	Number	Percent
Histology		
Lobular	1,182	8
Tubular	209	1
Ductal	14,328	91
Size (cm)		
⩽2	9,625	61
>2	6,094	39
⩽1	3,775	24
>1	11,944	76
⩽0.5	641	4
>0.5	15,078	96

TABLE II. Patient Characteristics for Group 2 (Total of 446 Patients From Area Hospitals)

Group 2	Number	Percent
Histology		
Lobular	47	11
Tubular	73	16
Ductal	326	73
Age		
<50	159	36
⩾50	287	64
NR	0	0
Diffferentiation		
Well	64	14
Moderate	131	29
Poor	57	13
NR	194	43
Estrogen receptor		
Positive	157	35
Negative	35	8
NR	254	57
LV invasion		
Positive	53	12
Negative	136	30
NR	257	58
S phase		
High	78	17
Low	106	24
NR	262	59

NR, not recorded by pathology; LV, lymphovascular.

variables (e.g., a small primary tumor size, diploidy, low S phase, etc.) would depend on the pathologic status of the axilla. If axillary dissections are not performed in this group of women, how reliably can we predict categories of risk for axillary involvement and at what level of risk are we willing to decide that the morbidity and costs of this procedure outweigh the benefits?

PATIENTS AND METHODS

Patient Characteristics

Breast cancer cases of the Colorado Cancer Registry were analyzed for the probability and extent of positive axillary lymph nodes calculated by tumor size (cm) and histology. A total of 15,845 patients with invasive breast cancer diagnosed from 1977 to 1995 were identified. Complete data concerning tumor size, number of dissected lymph nodes, pathologic status of the axilla, and histology were known for 15,719 patients, who form the basis for group 1. All patients underwent an axillary dissection (limited or complete) in addition to primary local breast surgery, which included either a radical or a modified radical mastectomy, quadrantectomy, or lumpectomy. Histologies were as follows: ductal, 14,328; lobular, 1,182; tubular, 209. Table I illustrates a breakdown of group 1 by tumor size and histology. A subgroup of 446 patients with ductal, lobular, and tubular histologies (group 2) was created from area hospitals (Swedish Medical Center, Lutheran Hospital, and Porter Hospital). Information from individual pathology reports and/or slides of this group was confirmed by the pathology departments of Swedish Medical Center (P.P.) and/or Rose Medical Center. The best gross and/or microscopic size assessment of invasive carcinoma was quantified as accurately as possible. An analysis of axillary involvement and the following variables was performed: age (less than 50 years vs. more than or equal to 50 for univariate analysis), differentiation (well vs. moderate vs. poor), estrogen receptor (ER, positive vs. negative), DNA ploidy (aneuploid vs. diploid), lymphovascular invasion (positive vs. negative), and S phase (high vs. low). Generally, DNA indices as well as estrogen receptor status were referred to outside laboratories. S phase was also reported by consultant laboratories utilizing their internally determined reference ranges (5.5–8%). Patient characteristics for this entire subgroup are shown in Table II. Patients with multifocal or multicentric ipsilateral carcinomas were included in this analysis (size of the largest site of disease was used for this purpose). Patients with ''microinvasive'' disease were excluded if a measurement of the invasive component could not be adequately assessed. To quantify the term ''low risk'' of axillary involvement, we chose a probability of less than 10% solely for the purposes of statistical analyses. Both groups 1 and 2 were examined to determine prognostic variables which correlated with axillary involvement (positive vs. negative) and predicted a less than 10% probability of axillary metastases or extent of axillary involvement if positive (number of positive nodes in a positive axillary dissection).

Statistical Analyses

Univariate analyses provided general descriptive results and were used as a screen for variable selection for multivariate methods. Categorical variables were tested by a two-sided Fisher's exact test. Continuous variables were tested by a two-sided, independent-samples *t*-test or a Wilcoxon rank-sum test, whichever was most appro-

TABLE III. Prevalence of Axillary Involvement in 15,719 Patients With Breast Cancer Identified From the Colorado Tumor Registry

	Lobular			Tubular			Ductal		
Size (cm)	Number	Positive (%)	*P* value	Number	Positive (%)	*P* value	Number	Positive (%)	*P* value
⩽2	653	165 (25)	1.8×10^{-30}	189	22 (12)	0.705	8,783	2,353 (27)	10^{-238}
>2	529	307 (58)		20	1 (5)		5,545	3,255 (59)	
⩽1	244	41 (17)	8.6×10^{-18}	143	14 (10)	0.477	3,388	586 (17)	8.4×10^{-212}
>1	938	431 (46)		66	9 (14)		10,940	5,022 (46)	
⩽0.5	40	5 (13)	2.1×10^{-4}	28	2 (7)	0.746	573	69 (12)	1.3×10^{-48}
>0.5	1,142	467 (41)		181	21 (12)		13,755	5,539 (40)	

priate. The level for statistical significance was $P = 0.05$.

Logistic regression was the multivariate method used to identify the final model. All variables which were significantly associated with the presence of positive lymph nodes in univariate analyses were included in the initial logistic regression model. In addition, selected paired interactions among tumor size, age, lymphovascular invasion, and clinically palpable nodes were included in the initial model. The model-building process of Hosmer and Lemeshow [2] was utilized. Stepwise regression was used, with entry and exit criteria of $P = 0.25$ as this was regarded as a hypothesis-generating model. The scales of continuous variables were evaluated for proper modeling by evaluation of nonlinear effects of the form *var**ln(*var*).

RESULTS

Group 1 Analysis of how Tumor Size, Number of Lymph Nodes Examined, and Histology Correlated With a Positive Axillary Dissection and/or Number of Positive Lymph Nodes

For group 1, frequencies of axillary metastases by histology were as follows: ductal, 39% (5,608/14,328); lobular, 40% (472/1,182); tubular, 11% (23/209) ($P = 0.001$). All size comparisons (⩽2 cm *v* >2 cm, ⩽1 cm *v* >1 cm, ⩽0.5 cm *v* >0.5 cm) for ductal and lobular histologies were significant for axillary involvement (Table III). The probability of axillary involvement was 41% (467/1,142) *v* 13% (5/40) ($P = 2.1\ 10^{-4}$), 46% (431/938) *v* 17% (41/244) ($P = 8.6\ 10^{-18}$), and 58% (307/529) *v* 25% (165/653) ($P = 1.8\ 10^{-30}$) for lobular cancers and 40% (5,539/13,755) *v* 12% (69/573) ($P = 1.3\ 10^{-48}$), 46% (5,022/10,940) *v* 17% (586/3,388) ($P = 8.4\ 10^{-212}$), and 59% (3,255/5,545) *v* 27% (2,353/8,783) ($P = 10^{-238}$) for ductal cancers, which were >0.5 cm *v* ⩽0.5 cm, >1 cm *v* ⩽1 cm, and ⩽2 cm *v* >2 cm, respectively. We were not able to demonstrate that the probability of axillary nodal metastases was significantly associated with increasing tumor size in patients with tubular histology. Tumors larger than 2 cm had a 5% (1/20) chance of involvement, in contrast to 12% (22/189) for primary tumors ⩽2 cm. This difference was not statistically significant ($P = 0.705$). Likewise, for tumor sizes of ⩽1 cm or ⩽0.5 cm, the percentages of axillary involvement were 10% (14/143) and 7% (2/28) vs. 14% (9/66) and 12% (21/181), respectively, for sizes >1 cm or >0.5 cm. Again, these differences were not statistically significant ($P = 0.477$ and 0.746, respectively).

The mean number of lymph nodes examined was 16, with a standard deviation of 7.4 in group 1. Increasing primary tumor size was significantly associated with an increasing mean number of dissected axillary lymph nodes [16.6 *v* 17.6 (<5 cm *v* ⩾5 cm), 16.4 *v* 17.5 (<3 cm *v* ⩾3 cm), 16.2 *v* 17.2 (<2 cm *v* ⩾2 cm), 16.2 *v* 16.8 (<1 cm *v* ⩾1 cm); $P = 0.001$] (Table IVA). Also, the mean number of dissected axillary lymph nodes was significantly greater for ductal *v* tubular histology (16.8 *v* 15.6, $P = 0.023$) (Table IVB). The mean number of involved axillary lymph nodes in each positive dissection increased significantly with primary tumor size as well [1.7 *v* 6.4 (<5 cm *v* ⩾5 cm), 1.2 *v* 4.3 (<3 cm *v* ⩾3 cm), 0.8 *v* 3.1 (<2 cm *v* ⩾2 cm), 0.4 *v* 2.3 (<1 cm *v* ⩾1 cm); $P = 0.001$]. The mean number of involved lymph nodes in a positive dissection correlated significantly with histology [tubular *v* ductal (0.3 *v* 2.1), $P = 0.0001$; ductal *v* lobular (2.1 *v* 2.7), $P = 0.0003$; tubular *v* lobular (0.3 *v* 2.7), $P = 0.0001$]. Upon multivariate analysis, increasing tumor size and number of dissected lymph nodes were also found to be independent variables for the number of involved axillary lymph nodes in each positive dissection ($P = 0.0001$ for each variable).

Group 2 Analysis by Age, Differentiation, Lymphovascular Invasion, ER Status, S Phase, and DNA Ploidy

Possibly due to the small number of patients especially in tubular and lobular histologies, we were able to show only that age, lymphovascular invasion, and differentiation of ductal carcinoma patients as well as age and S phase of tubular carcinoma patients were significantly associated with axillary status. However, only age and S phase in tubular carcinoma and differentiation in ductal carcinoma were associated with a less than 10% probability of axillary involvement.

Age (<50 vs. ⩾50), differentiation, lymphovascular

TABLE IVA. All Comparisons Between Tumor Size Are Significant (P = 0.0001) for the Number of Positive Nodes and the Number of Examined Nodes in Group 1 (Total of 15,719 Patients From the State of Colorado Cancer Registry

Tumor size (cm)	Number	Number of positive lymph nodes		Number of examined lymph nodes	
		Mean	Standard deviation	Mean	Standard deviation
<5	14,322	1.7	4.0	16.6	7.2
⩾5	1,397	6.4	7.7	17.6	8.6
<3	11,022	1.2	3.2	16.4	7.0
⩾3	4,697	4.3	6.4	17.5	8.0
<2	6,778	0.8	2.6	16.2	6.9
⩾2	8,941	3.1	5.6	17.2	7.7
<1	1,959	0.4	2.1	16.2	7.1
⩾1	13,760	2.3	4.9	16.8	7.4

TABLE IVB. All Comparisons of the Mean Number of Positive Lymph Nodes Are Significant in Group 1 (Total of 15,719 Patients From the State of Colorado Cancer Registry)

Histology	Number	Number of positive lymph nodes		Number of examined lymph nodes	
		Mean	Standard deviation	Mean	Standard deviation
Ductal	14,328	2.1	4.6	16.8	7.4
Lobular	1,182	2.7	5.7	16.4	7.2
Tubular	209	0.3	1.1	15.6	7.1

Ductal vs. lobular, $P = 0.0003$; ductal vs. tubular, $P = 0.0001$; lobular vs. tubular, $P = 0.0001$. Only the comparisons between ductal and tubular histologies are significant in the number of examined lymph nodes ($P = 0.023$).

invasion, ER status, S phase, and DNA ploidy were examined in group 2 for prognostic significance of axillary involvement (Table V). Patients less than 50 years of age had positive axillary dissections in 13% (1/8), 40% (10/25), and 41% (48/117) for lobular, tubular, and ductal histologies, respectively. This contrasted with axillary involvement in 12% (3/26), 9% (3/32), and 27% (55/207), respectively, for patients older than or equal to 50 years of age. The differences for tubular and ductal histologies were statistically significant ($P = 0.01$ and 0.005, respectively). The percentage of axillary involvement according to differentiation was as follows: lobular 0% (0/3, well), 0% (0/4, moderate), 100% (1/1, poor) ($P = 0.125$); tubular 22% (2/9, well), 50% (1/2, moderate) ($P = 0.49$); ductal 7% (3/46, well), 33% (40/123, moderate), and 54% (30/56, poor) ($P = 7.5\ 10^{-7}$). Lymphovascular invasion was significantly associated with axillary involvement in ductal histology only. Fifty-six percent (28/50) of patients with lymphovascular invasion had positive axillary dissections, whereas 21% (23/108) had axillary involvement if there was no lymphovascular invasion ($P = 2.3\ 10^{-5}$). In tumors with lymphovascular invasion, one lobular carcinoma patient did not have an involved axilla; however, one tubular carcinoma patient did have a positive axilla. Two of four lobular carcinoma patients and 3 of 17 tubular carcinoma patients without lymphovascular invasion had positive axillary dissections ($P = 1$ and 0.22, respectively). ER status was not a significant factor for axillary involvement in any histology. Axillary dissections of ER-positive lobular, tubular, and ductal histologies were positive in 10% (1/10), 22% (5/23), and 32% (39/122) of cases, respectively ($P = 1.0$, 1.0, and 0.42, respectively). Neither lobular nor tubular ER-negative patient had a positive axilla. Thirty-nine percent (13/33) of ER-negative ductal carcinoma patients had axillary involvement. S phase was significantly associated with axillary involvement only in tubular carcinoma. Sixty-seven percent (2/3) of cases with a high S phase compared to none with a low S phase had axillary involvement (0/14 low, $P = 0.022$). S phase was not a significant predictor for axillary involvement in either lobular or ductal histologies. Lobular or ductal histologies with a high S phase had axillary involvement in 11% (1/9) and 30% (20/66) of cases, respectively, in contrast with 20% (1/5) and 35% (29/84) if the S phase was low ($P = 1$ for lobular and 0.6 for ductal). DNA ploidy was not significantly associated with axillary involvement for any histology. Axillary dissections of diploid lobular, tubular, and ductal histologies were positive in 13% (1/8), 6% (1/16), and 34% (32/95) of cases, respectively, vs. 29% (2/7), 50% (1/2), and 33% (21/63) for aneuploid tumors ($P = 0.57$, 0.22, and 1.0, respectively).

Multivariate Analysis and Construction of the Final Multivariate Model for the 446 Group 2 Cases

Table VI illustrates that tumor size, measured on a continuous scale, was more significantly associated with axillary involvement than any other variable ($P = 0.001$). Several multivariate models were evaluated for a relationship with axillary involvement. As noted in Figure 1, the inclusion of tumor size and age proved to be the best model to describe axillary involvement. To minimize the number of missing values, this model evaluated only the variables of age, tumor size, histology, and the paired age–tumor size interaction. From a total sample size of 446, there were 401 patients who had complete data for these variables. The number of patients with positive and negative lymph nodes was 112 and 289, respectively.

Stepwise logistic regression returned a final model containing an intercept, tumor size, and age. Histology and the age–tumor size interaction were not statistically significant. The odds ratios for age and tumor size are shown in Table VI, along with 95% confidence intervals. Since tumor size and age are continuous variables, the

TABLE V. Prevalence of Axillary Metastases in Group 2 (Total of 446 Patients From Area Hospitals) Correlated With Other Prognostic Factors

	Lobular (n = 47)			Tubular (n = 73)			Ductal (n = 326)		
Variable	n	Positive (%)	*P* value	n	Positive (%)	*P* value	n	Positive (%)	*P* value
Age (years)									
<50	8	1 (13)	1.00	25	10 (40)	0.010	117	48 (41)	0.005
⩾50	26	3 (12)		32	3 (9)		207	55 (27)	
Differentiation									
Well	3	0		9	2 (22)		46	3 (7)	
Moderate	4	0	0.13	2	1	0.49	123	40 (33)	7.5×10^{-7}
Poor	1	1		0	N/A		56	30 (54)	
LV invasion									
+	1	0	1.00	1	1	0.22	50	28 (56)	2.3×10^{-5}
−	4	2 (50)		17	3 (18)		108	23 (21)	
Diploid	8	1 (13)	0.57	16	1 (6)	0.22	95	32 (34)	1.0
Aneuploid	7	2 (29)		2	1		63	21 (33)	
ER^+	10	1	1.00	23	5 (22)	1.00	122	39 (32)	0.42
ER^-	1	0		1	0		33	13 (39)	
S phase									
High	9	1 (11)	1.00	3	2 (67)	0.022	66	20 (30)	0.60
Low	5	1 (20)		14	0		84	29 (35)	

n, number; ER, estrogen receptor; LV, lymphovascular.

TABLE VI. Multivariate Analysis of Group 2 Patients (Total of 446 Patients From Area Hospitals)

Parameter	Odds ratio	*P* value	95% Confidence intervals
Tumor size (cm)	1.036	0.00034	1.016–1.057
Age (years)	0.986	0.2236	0.964–1.009

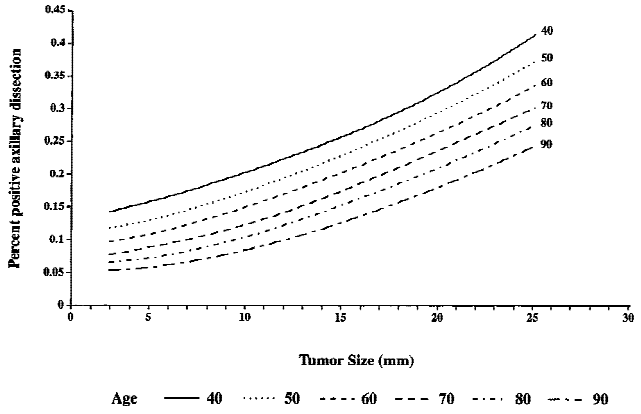

Fig. 1. Final multivariate model analysis of 401 group 2 patients (from area hospitals) by age and tumor size.

odds ratios are interpreted to be the increase in risk for one unit increase in the variable. Increasing tumor size was associated with increased risk of positive nodes, whereas increasing age was associated with a decreased risk of positive nodes: logit(y) = −1.1719 + 0.0645*tumors − 0.0183*age. The sensitivity and specificity corresponding to axillary involvement probability are given in Table VII.

DISCUSSION

In patients with clinically negative axillae, evidence of axillary involvement will later manifest as clinical axillary progression in as high as 19–20% of cases if untreated [1]. However, performing an axillary dissection can lower this to nearly zero. If the probability of occult axillary involvement cannot be accurately predicted, categories of women will be erroneously codified as having a low risk of axillary involvement. Consequently, there may be an increase of axillary/supraclavicular failures in patients whose axillae are not surgically dissected. Elective axillary irradiation has been another effective alternative in preventing axillary disease progression in clinically negative and undissected axillae. However, this technique is not without its own morbidity risks, such as match line fibrosis, pneumonitis (especially in women receiving concurrent chemotherapy), and arm edema [1]. A number of reports have documented our inability to accurately determine axillary status by physical examination. False-negative results range 27–30% [3–6].

Presently, however, the necessity of an axillary dissection has been questioned in women with small breast cancers of all histologies, especially tubular. Many studies have had various results when attempting to correlate the probability of axillary metastases with other clinical or prognostic variables [7–22]. Tumor size, or more precisely size of the invasive component when mixed with noninvasive cancer, has been found to correlate with the probability of axillary involvement [7–10]. However,

TABLE VII. Table of Associated Modeled Risk Analysis (From Fig. 1) With Probability, Sensitivity, and Specificity for Axillary Involvement, Which Includes Tumor Size and Age

Probability level	Sensitivity	Specificity
0.01	100.0	0.0
0.02	100.0	0.0
0.03	100.0	0.0
0.04	100.0	0.0
0.05	100.0	0.0
0.06	100.0	0.0
0.07	100.0	0.0
0.08	100.0	0.0
0.09	100.0	0.7
0.10	99.1	2.4
0.11	97.3	4.2
0.12	97.3	8.3
0.13	97.3	13.1
0.14	95.5	18.7
0.15	92.9	22.1
0.16	88.4	28.4
0.17	84.8	34.3
0.18	82.1	39.1
0.19	80.4	43.6
0.20	75.9	49.1
0.21	74.1	54.0
0.22	68.8	57.4
0.23	67.9	63.3
0.24	67.9	65.1
0.25	67.0	67.5
0.26	64.3	69.6
0.27	62.5	73.4
0.28	58.9	76.1
0.29	58.0	78.9
0.30	54.5	81.3

whether or not there is a size at which this risk becomes insignificant is a matter which is currently debated [1,22]. Many other variables have been analyzed separately or combined with tumor size (e.g., grade, differentiation, DNA ploidy, neovascularization, S phase, parity, number of pregnancies, and mammographic vs. clinical findings) to determine significant factors for axillary involvement. These studies have resulted in a number of various, though not necessarily contradictory, results [11–22].

In both of our patient group analyses, we found that tumor size correlated significantly with the probability of axillary involvement in cases of lobular and ductal histologies ($P = 0.0001$). This is a finding which was similar to other reported series examining the relationship of increasing primary tumor size and the risk of axillary involvement. However, our results could not identify a primary tumor size at which the probability of axillary involvement was less than 10% and at a level of statistical significance. Upon further subset analysis, we were able to show significant associations only with age ($P = 0.005$), lymphovascular invasion ($P = 2.3\ 10^{-5}$), and differentiation ($P = 7.5\ 10^{-7}$) of ductal carcinoma patients as well as age ($P = 0.01$) and S phase ($P = 0.022$) of tubular carcinoma patients. Only well-differentiated ductal histologies and tubular cancer patients less than 50 years of age or with a low S phase were found to have axillary involvement in less than 10% of cases (significant at $P < 0.05$). As stated earlier, our failure to prove any other significant correlations may be a result of a low number of patients with known variables, especially in the lobular and tubular histologies subset analysis.

Although our results show that tubular cancers of the breast have a significantly lower percentage of axillary metastases than either lobular or ductal histologies ($P = 0.001$), we were unable to show that this was less than a 10% risk. Size did not prove to be a reliable indicator of axillary involvement for tubular histology in either group 1 or group 2. Both age greater than 50 and low S phase were significantly associated with a less than 10% risk of axillary involvement in tubular histology. However, the small number of tubular cases in our series may have weakened our ability to show other significant correlations. These conclusions may illustrate that our rationale and accuracy at predicting the probability of axillary metastases might be poor. Many practitioners believe that tubular breast carcinoma has a lower risk of axillary involvement and a universally good outcome whether the axilla is involved or not. The only two studies which specifically addressed the risk of axillary involvement in tubular carcinoma of the breast have reported conflicting results. Although McDivitt et al. [23] found that a mean tumor size of 1.5 cm was significant for axillary involvement, Elson et al. [24] reported that metastatic axillary carcinoma was found in four of 14 (29%) patients with tubular cancer and a median size of 8 mm.

These data help to illustrate that we must be prudent in our confidence to accurately discern patients who would have a ''minimal'' risk of axillary metastases. Moreover, what should we consider being minimal risk: 11%, 12%, 13%? Possibly, the question should be whether the results of an axillary dissection will decide or alter adjuvant therapies, not calculating the probability of a positive axillary dissection. All of these arguments have heightened the question of whether an axillary dissection is needed in all women. Clinically node-negative women with adverse primary tumor characteristics (e.g., aneuploidy, high S phase, negative ER status, poor differentiation, or lymphovascular invasion) may not benefit from the results of an axillary dissection. Adjuvant therapy for this group of patients already may have been decided. However, it could be argued that the information from a positive dissection may ultimately prove to be useful. The number of positive lymph nodes could determine the type and/or intensity of adjuvant therapy (e.g., cyclophosphamide/methotrexate/fluorouracil vs. cyclophosphamide/doxorubicin/fluorouracil vs. high-dose chemotherapy followed by bone marrow/stem cell

transplantation). If the results of an axillary dissection might dictate adjuvant therapy and/or its type, there must be more definitive information which aids practitioners to codify categories of increasing risk of axillary involvement. It was very interesting to note that in our analysis the size of the primary tumor correlated significantly with the number of metastatic axillary lymph nodes in a positive dissection independent of the number of nodes examined. Therefore, it might be possible to also categorize groups of women by risk of axillary involvement and/or increasing numbers of metastatic axillary lymph nodes.

In group 2, we constructed a final multivariate model of age and tumor size which was found to best predict probability of axillary metastases. Although similar to the model of Holmberg et al. [19], we formatted our multivariate model so that a probability of axillary metastases and their predictive values might be more readily apparent. As authors, we are not presenting this modeled analysis of our regional community practice as a paradigm for other communities. The decision to perform an axillary dissection eventually may evolve into an algorithm which includes a consideration of how it may determine adjuvant therapy. This might also include a modeled probability risk analysis for sensitivity and/or specificity of axillary involvement according to known salient clinical factors (e.g., Table VII and Figure 1). A model such as we have described could be formulated in any community practice and used in the decision tree to determine which patients would then be at a risk which was high enough to warrant axillary staging. For example, a clinician may choose that a 10% risk of axillary involvement with an associated sensitivity of 99.1% and specificity of 0.7% is acceptable clinical practice. From the corresponding graph, the portions of each curve beneath a horizontal line at 0.10 probability would show the group of patients who would not have an axillary staging procedure. In contrast, portions of the curves above the line would have an axillary staging procedure. A 40- or 50-year-old patient with a tumor size of 5 mm would have surgical axillary staging, whereas a 70-, 80-, or 90-year-old patient would not. From our model, this would mean that more than 99% of women with pathologically positive axillae would undergo an axillary staging procedure. However, at this 10% probability level, the specificity would be extremely low. The result would be that 97.6% of pathologic node-negative women would undergo a needless, very invasive staging procedure. Women at this 10% probability level or greater might proceed to lesser surgical staging techniques, such as sentinel node biopsy, which has recently been described as a very accurate method of sampling the axilla [25]. Giuliano et al. [25] have reported that this technique has an amazing 100% predictive value in staging the axilla in women with carcinoma of the breast without the associated morbidity of an axillary dissection. A substantial number of pathologic node-negative women could avoid such untoward sequelae associated with a full or limited axillary dissection. This information could also mollify concerns of axillary failure in clinically node-negative women with undissected/unirradiated axillae. With such a modeled analysis we would be able to accurately decide at which level of probability we are willing to omit an axillary dissection (or any axillary therapy) and assess the consequence of such an en masse practice management.

As discussed above, our data also show that some women who have a primary cancer size (e.g., 2.5–3 cm) large enough to be at risk for a positive axillary dissection may also be at risk for a large number of involved lymph nodes. These women might forego the sentinel node biopsy and proceed directly to an axillary dissection. In this way, information for therapy decisions would involve a single procedure. A premenopausal 40-year-old woman with a 3 cm breast primary might proceed directly to an axillary dissection. Not only would her risk of involved nodes be exceedingly high but the risk of having more than four positive axillary nodes would also be significantly high (mean number of involved lymph nodes 4.3 *v* 1.2 for primary tumor size of $\geqslant$3 cm *v* <3 cm). A large number of involved nodes might qualify her for a high-dose, intensive adjuvant systemic therapy regimen. Also, the possibility of a multiple number of positive lymph nodes might require more than a sentinel node procedure. An adequate limited axillary dissection should be performed because, as we have shown, the number of dissected nodes in a positive dissection correlates with the number of positive nodes. This could prove to be vital information (number of positive lymph nodes) for therapy decisions, as mentioned above. Our results are similar to those of Fisher et al. [26], who found that qualitatively the extent of dissection does not significantly change the status of an axilla (positive vs. negative). In contrast, the extent of dissection, or number of dissected lymph nodes, significantly increased the percentage of women with four or more positive lymph nodes. Conversely, if her primary were 1.0 cm, then, although she may not be at a significant risk for a large number of involved lymph nodes, she would in any case be at risk for a positive dissection. Therefore, if axillary information (involved *v* uninvolved and/or number of metastatic lymph nodes) would be pertinent for therapy decisions, a sentinel node biopsy could be the initial procedure. If this were positive, then it could be followed by an axillary dissection.

Obviously, a drawback to our retrospective community clinical review is that there was not an independent pathologic review of our cases. One pathologist (P.P.) from Swedish Medical Center and a group practice at Rose Medical Center were primarily responsible for the

data attained in group 2, and those of group 1 were drawn strictly from the Colorado State Cancer Registry Database. Despite our work, we realize that such modeled analyses demand larger numbers of patients evaluated in rigorously conducted prospective studies. However, we hope that this work will stimulate research in this area to combine an analytical model with different levels of axillary staging techniques. This might help to discriminate patients who would require minimal vs. more invasive staging procedures yet still reveal information necessary for therapy decisions.

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